FEATURED EDITORIAL

# Raising awareness of angina in women

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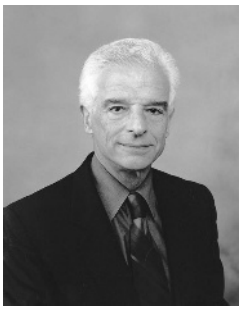
"If ischaemic heart disease affects women differently from men, then our diagnostic testing, risk stratification schemes and treatment modalities should be sexist as well"



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After decades of denial, increasing attention has recently been focused on ischaemic heart disease (IHD) in women. It is now accepted that IHD is the leading cause of mortality fewer a leading cause of morbidity in women. Women present later for medical attention, receive fewer diagnostic investigations and are less likely to be treated with established therapies than men. But these findings are unlikely to fully explain the poor prognosis of women after myocardial infarction or revascularisation, or those with heart failure. The enigma is compounded by repeated documentation of less frequent flow-limiting stenoses on angiography among women presenting with signs and symptoms suggesting IHD compared with men.[1] These findings implore us to shift our focus and intensify exploration of the gender differences in the IHD process.

## AETIOLOGICAL DIFFERENCES COMPARED WITH MEN

Aetiological differences in IHD between men and women are clearly multifactorial and have only recently been emphasised. Interplay of traditional and non-traditional risk factors, hormonal variations, and differences in vascular structure and function contribute to development of a somewhat different form of disease. Small coronary arteries, diffuse disease and microvascular dysfunction are frequent among women.[2 3] As new data emerge, these factors have increasingly significant implications for diagnosis, prognosis, and treatment.

Traditional risk factors such as hypertension, obesity, diabetes, etc, tend to occur more frequently and cluster more often in postmenopausal women than in men of similar age. Some factors independently increase risk more in women compared to men—for example, among diabetics, women tend to have worse outcomes than men.[4] Hypertriglyceridaemia and metabolic syndrome also confer increased risk in women compared to men.[5 6] Overall, women tend to have a lower functional status, which may contribute to weight gain, insulin resistance and diabetes, and hypertension.[3 7 8] In the Women's Ischemia Syndrome Evaluation (WISE), we have found that functional capacity, estimated from the Duke Activity Status Index (DASI), provides a simple, rapid measure closely linked with adverse outcomes and coronary microvascular dysfunction.[9 10]

A link clearly exists between female-unique conditions and elevated IHD risk.[8] Delivering a low birth weight child, hypertensive disorders of pregnancy, and gestational diabetes appear linked to elevated risk, perhaps via inflammation and oxidative stress. Hypoestrogenaemia of central origin, polycystic ovarian syndrome, and early age at menopause convey elevated risk via hormonal influences, particularly in younger women.

Other conditions more frequent in women than men, such as vasculitis and vasospastic disorders (for example, Raynaud's phenomenon, migraine, etc), are also linked to increased IHD risk. Factors influencing development of IHD and its consequences such as vessel size, remodelling, and function appear influenced by sex hormones. Female vessels are smaller and become less elastic as aging occurs compared with men. Reduced arterial compliance, as reflected in pulse pressure, was a robust independent clinical predictor of adverse outcomes in the WISE study.[11]

Unlike men, a woman's coronary arteries are exposed to wide variations in sex hormone concentration over her lifetime. Estrogen values, predominantly estradiol, are high before menopause. During menopause, these values fall dramatically and the dominant source of estrogen becomes estrone, formed from androgens. Androgen excess has been linked to positive arterial remodelling, a potential substrate for unstable plaque formation.

Endothelial and smooth muscle cell (SMC) dysfunction contribute to a microvascular disorder frequently observed in women with signs and symptoms of IHD and angiographically normal coronary arteries. Over half of the WISE participants tested demonstrated endothelial dysfunction with acetylcholine. Lower concentrations of estrogen and a reduced ability for endothelial repair later in life likely contribute to the delayed presentation of women with IHD, compared to men.[12]

Recently, it has been suggested that the vascular SMC phenotype is regulated by the activational state of estrogen receptor-α (ESR1). This could explain how the balance between a highly differentiated SMC, capable of maintaining the extracellular matrix and structure of the arterial wall, changes to a less differentiated SMC that is apoptotic and leads to positive remodelling and unstable plaques.[13] In addition, dysfunctional SMCs could contribute to a microvascular disorder characterised by impaired relaxation and remodelling of the perfusion vessels. Such processes may

**Abbreviations:** DASI, Duke Activity Status Index; ESR1, estrogen receptor-α; IHD, ischaemic heart disease; PChP, persistent chest pain; SMC, smooth muscle cell; WISE, Women's Ischemia Syndrome Evaluation

contribute to the differences in outcomes observed between women and men with acute coronary syndromes, revascularisation and heart failure.

## OUTCOMES AS REFLECTED IN RECENT OBSERVATIONS

Not only do women presenting for evaluation of suspected IHD receive less angiography, but they also have a higher incidence of recurrent chest pain and rehospitalisation for chest pain. We have found that even among women who had angiography and were shown to have normal coronary arteries, half will continue to have persistent chest pain (PChP) at one year follow-up.[14] Those with PChP tend to be younger but have diminished functional capacity when compared to women without PChP. These women also have a higher incidence of depression, probably related to their chronic pain symptoms.

Unfortunately, women with PChP despite normal coronary arteries tend to have a worse prognosis than those without PChP. In the WISE study, women with normal coronary angiography and PChP were at a twofold increased risk for adverse events, including death, compared to women with normal angiography who did not report PChP. The presence of PChP was linked with a cardiovascular event in 57% of women with normal angiography. This link between PChP and cardiac events was not seen in women with obstructive coronary disease, probably because those women were more aggressively managed with risk factor modification and other strategies known to reduce risk.

Assessing cardiovascular risk in women is challenging. Previous models to risk stratify patients do not apply particularly well to women. Recently we have found that a multimarker panel composed of haemoglobin and high sensitivity C reactive protein, serum amyloid A and interleukin-6 were useful in predicting cardiovascular events.[15]

## TREATMENT IMPLICATIONS

If half of women with PChP but angiographically normal coronaries will have adverse cardiovascular events in the future, the reference standard coronary angiography must be augmented with additional testing to evaluate the microvasculature and perhaps the state of inflammation. Provocative testing for spasm and endothelial dysfunction during angiography, single photon emission computed tomography and/or cardiac magnetic resonance perfusion should be performed in women with angiographically normal coronary arteries, who continue to have chest pain.[3]

These women should not only undergo traditional risk factor modification, like their cohorts with abnormal angiography, but should also be closely monitored for future ischaemic sequelae and aggressively medically managed. Treatment should be aimed at managing not only the PChP itself, but the accompanying psychological effects as well. Treatment regimens that need to be better studied in this subset of women include standard anti-ischaemic agents as well as angiotensin-converting enzyme inhibitors and statins. Other measures that may prove useful include exercise training, L-arginine, and imipramine.

The presence of PChP should be considered an additional cardiovascular risk factor. The presence of normal coronary angiography should not be taken as a negative risk factor that encourages practitioners to rest assured that the PChP is non-cardiac. PChP must be considered cardiac until proven otherwise, but a coronary angiogram without a flow-limiting obstruction is not proof in a woman with signs and symptoms of IHD. Clearly, if IHD affects women differently from men, then our diagnostic testing, risk stratification schemes and treatment modalities should be sexist as well.

## CONCLUSIONS

Compared to men, IHD in women tends to cause more death and disability and microvascular dysfunction, making the diagnosis challenging and necessitating novel management approaches to women with angina.


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